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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/821,653	04/09/2004	Paul D. Coleman	21108.0060U4	8802

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NEEDLE & ROSENBERG, P.C.
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ATLANTA, GA 30309-3915

EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	**PAPER NUMBER**
1636	

MAIL DATE	DELIVERY MODE
10/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/821,653	COLEMAN ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 57-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 57-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/11/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment, filed 7/11/2007, in which claim 1 was amended, and claims 57-60 were newly added. Currently, claims 1 and 57-60 are pending.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

Priority

It is noted that this application appears to claim subject matter disclosed in prior Application Nos. 09/770,534 and 09/178,170 and provisional application 60/063,274. A reference to the prior application must be inserted as the first sentence(s) of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e), 120, 121, or 365(c). See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, 121, or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months

from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

It is noted that the reference to the prior filed applications was made at page 1, line 9. This is not the first sentence of the specification. Furthermore, the status of the nonprovisional applications should be included.

Applicant's petition to accept an unintentionally delayed claim for priority was dismissed on 9/11/2007. The wording of the claims for benefit of priority is improper since the claim, as presented, states that Application No. 09/178,170 claims benefit to a later-filed provisional application (60/179,214). Further, Application No. 09/770,534 fails to disclose that a claim for priority was ever made to provisional Application No. 60/179,214. See the petition decision mailed 9/11/2007.

Information Disclosure Statement

The information disclosure statement filed 7/11/2007 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because dates were not provided for the references as required by 37 CFR 1.98(b)(5). It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Claim Objections

Claims 1 and 57 are objected to because of the following informalities: the term "1-ACT" should be "α1-ACT" to be consistent with the nomenclature used in the specification for the α_1-antichymotrypsin gene (e.g., page 20, line 27; page 32, line 4). Claims 58-60 depend from claim 1 and thus are objected to for the same reason applied to claim 1. Appropriate correction is required. This is a new objection necessitated by the amendment of the claims in the reply filed 7/11/2007.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 57-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is a new rejection, necessitated by the amendment of claim 1 and addition of new claims 57-60.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The claims are drawn to a "method of profiling mRNA production during stages." The method is drawn to the steps of (i) isolating a plurality of cells from a subject, (ii) analyzing the mRNA production in the cells from the subject, wherein the mRNA encode two or more genes selected from the group consisting of α1-ACT, cyclin D1, HSP27, wee1, GAD and HES1, (iii) quantitating the levels of the mRNA, and (iv) comparing the levels of mRNA in the subject to a control. Claim 57 limits the genes to two or more genes selected from the group consisting of α1-ACT, cyclin D1, HSP27 and wee1. Claim 58 limits the subject to one that is in need of a diagnosis of a degenerative disease. Claim 59 limits the degenerative disease to Alzheimer's disease. Claim 60 limits the sample to a blood sample collected from a living patient.

The nature of the invention is complex in that the gene expression levels must be indicative of the diagnosis or staging of a disease—the only disclosed use for the claimed invention.

Breadth of the claims: The claims are broad in that they encompass any subject of any species of organism, any type of sample, and any increase or decrease in expression of the recited combinations of genes. Further, the claims are broad in that they encompass every possible combination of two or more genes selected from the group consisting of α1-ACT, cyclin D1, HSP27, wee1, GAD and HES1. The phrase "during stages" in the preamble can reasonably be interpreted as stages of development, or stages of any type of disease. Thus, the method broadly encompasses the determination of any developmental disease stage, the presence or absence of any disease, and the determination of severity of any disease. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

Guidance of the specification and existence of working examples: The specification envisions the comparison of gene expression profiles for the diagnosing or monitoring the progression of a disease (e.g., pages 18-19). The specification envisions using any sample from a living patient, including brain tissue (from a living individual or postmortem), blood, cheek scrapings, cerebral spinal fluid, saliva, urine, and skin (e.g., page 22, lines 3-4; page 27, lines 8-10). The specification envisions the diagnosis or monitoring of virtually any disease: infections by bacteria, fungi, or viruses, genetic disease, autoimmune disease, and degenerative disease such as Alzheimer's disease (e.g., page 28, lines 8-13).

The working examples of the specification teach the analysis of gene expression of twenty genes in neurons sampled from early and late stage Alzheimer's disease (AD) of post mortem AD brains (e.g., page 47, lines 16-21). Seven cells were tested in duplicate for each brain and two early AD and three late AD brains were tested (e.g., page 47, lines 16-21; page 51, lines 17-20). Using ANOVA, five genes were found to be significantly different between the two groups: α1-ACT, cyclin D1, HSP27, wee1, GAD and HES1 ($p<0.05$) (e.g., paragraph bridging pages 51-52). The specification asserts that cyclin D1, HSP27, and GAD were significantly decreased in late stage AD while α1-ACT and wee1 were significantly increased in late AD (e.g., paragraph bridging pages 51-52).

The specification does not teach the measurement of mRNA levels of α1-ACT, cyclin D1, HSP27, wee1, GAD and HES1 in any disease other than Alzheimer's disease. The specification does not teach the expression levels of these genes in individuals without AD. The specification does not teach the expression level of α1-ACT, cyclin D1, HSP27, wee1, GAD and HES1 in any sample other than neurons from human postmortem brain.

Predictability and state of the art: The art teaches that gene expression analysis is commonly used for three different purposes: (1) as a screening tool to identify individual genes of interest that might contribute to an important biological function, (2) to obtain insight into an important biological function, and (3) as a classification tool to sort cases into clinically important categories (Pusztai and Hess. Annals of Oncology, Vol. 15, pages 1731-1737, 2004; e.g., paragraph bridging pages 1732-1733). In the instant case, the specification uses gene expression analysis to identify genes that are differentially expressed in neurons from a small sample of postmortem AD brains. Thus, the specification uses the gene expression analysis as a screening tool to identify genes or provide insight into AD. However, the claims are drawn to using gene expression analysis to either diagnose or monitor any disease from any subject in any sample type. Pusztai and Hess teach that validation of gene expression important to biological function may be validated by using different methods, such as RT-PCR, whereas the most appropriate validation for using gene expression analysis as a classification tool is testing the predictor on independent sets of cases (e.g., page 1733, left column, 1st full paragraph). In the instant case the specification does not teach the predictive value of the mRNA expression for the gene combinations recited in the claims for the classification of any individual into any disease stage.

Further, Shalon et al (US 2001/0051344 A1, Dec 13, 2001) teach that due to variations in genetic make-up of unrelated individuals in a heterogeneous society, differences in the expression of a gene between any two individuals may or may not be significant (e.g., paragraph [0155]). Shalon et al further teach that the larger the number of individuals tested, the more significant the remaining differences in gene expression become and samples from at least 5 and

preferably 20-50 different test individuals are assayed to obtain statistically meaningful data showing a statistical elevation or reduction in report levels when compared to control levels (e.g., paragraph [0156]). Pusztai and Hess teach that larger samples sizes may be needed to validate classification tests, and the number of samples will vary depending upon the acceptable error rates, level of inter-patient variability, the size of the difference in mean expression values, and the prevalence of the phenotype among the group being tested (e.g., page 1734, paragraph bridging columns; Table 1). The instant specification teaches that a major source of variation in gene expression levels is the method of detection (62%), yet within- and between-sample variation does exist (e.g., paragraph bridging pages 33-34).

Genetic tests are heterogeneous in nature and the exact characteristics of a particular genetic test to be evaluated must be tightly defined (Kroese et al (Genetics in Medicine, Vol. 6, pages. 475-480, 2004). Kroese et al teach that genetic test is shorthand to describe a test to detect a particular genetic variant for a particular disease in a particular population and for a particular purpose and that it should not be assumed that once the characteristics of a genetic test are evaluated for one of these reasons that the evaluation will hold or be useful for other purposes and all measures of the test performance should be presented with their 95% confidence intervals (e.g., page 477, 1st column, 1st and 2nd full paragraph). Kroese et al teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are likely to be gaps in the information needed to complete a thorough evaluation of many genetic tests (e.g., page 479, 2nd column, last paragraph).

Even within AD, the expression of the recited genes is not necessarily consistent. For example, Renkawek et al (Acta Neuropathol, Vol. 87, pages 511-519, 1994) teach that heat-

shock protein 27 (hsp27) is expressed to a greater extent in late AD as compared to control brains and patients with shorter dementia (e.g., pages514-515, Expression of hsp 27 in AD-affected brains). This contrasts with the teachings of the specification. The specification asserts that HSP27 is decreased in late AD as compared to early AD (e.g., paragraph bridging pages 51-52). Accordingly, it would be unpredictable to extrapolate the gene expression results of the specification to classify individuals. Furthermore, it would be unpredictable to extrapolate the expression results to other cell types and other diseases.

Amount of experimentation necessary: Given the lack of guidance in the specification and prior art with regard to diagnosing or staging using the mRNA expression levels of the claimed combination of genes, the quantity of experimentation in this area is very large. Due to the small sample sizes used and the use of only neurons from only early and late AD postmortem brain, one would not know how to use the claimed invention for the diagnosis or staging of AD or any other disease. The nature of the guidance in the specification is not specific enough to allow one to practice the claimed invention for the analysis of any stage of development or disease. For one to use the claimed invention, one would be required to perform a large amount of experimentation, with the success of one combination of genes for one particular stage not providing any guarantee of success with any other stage or disease.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 1 and 57-60 are not considered to be enabled by the instant specification.

Response to Arguments - 35 USC § 112

The rejection of claim 1 under 35 U.S.C. 112, second paragraph, has been withdrawn in view of Applicant's amendment to the claims in the reply filed 7/11/2007.

Response to Arguments - 35 USC § 102

The rejection of claim 1 under 35 U.S.C. 102(b) as being anticipated by Musselman et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 7/11/2007.

The rejection of claim 1 under 35 U.S.C. 102(b) as being anticipated by Eberwine et al (The Neuroscientist, Vol. 1, No. 4, pages 200-211, 1995) has been withdrawn in view of Applicant's amendment to the claims in the reply filed 7/11/2007.

The rejection of claim 1 under 35 U.S.C. 102(e) as being anticipated by Eberwine et al (US Patent No. 5,723,920) has been withdrawn in view of Applicant's amendment to the claims in the reply filed 7/11/2007.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached at 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston, Ph.D.
Examiner
Art Unit 1636

/JD/

CELINE QIAN, PH.D.
PRIMARY EXAMINER